Effect of expiratory resistive loading on the noninvasive tension-time index in COPD

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Thompson, William H., Paula Carvalho, James P. Souza, and Nirmal B. Charan. Effect of expiratory resistive loading on the noninvasive tension-time index in COPD. J Appl Physiol 89: 2007–2014, 2000.—Expiratory resistive loading (ERL) is used by chronic obstructive pulmonary disease (COPD) patients to improve respiratory function. We, therefore, used a noninvasive tension-time index of the inspiratory muscles (TTmus = P0.1/TI × T0.1/T0, where P0.1 is mean inspiratory pressure estimated from the mouth occlusion pressure, P1 is maximal inspiratory pressure, TI is inspiratory time, and T0 is total respiratory cycle time) to better define the effect of ERL on COPD patients. To accomplish this, we measured airway pressures, mouth occlusion pressure, respiratory cycle flow rates, and functional residual capacity (FRC) in 14 COPD patients and 10 normal subjects with and without the application of ERL. TTmus was then calculated and found to drop in both COPD and normal subjects (P < 0.05). The decline in TTmus in both groups resulted solely from a prolongation of expiratory time with ERL (P < 0.001 for COPD, P < 0.05 for normal subjects). In contrast to the COPD patients, normal subjects had an elevation in P0.1 and FRC, thus minimizing the decline in TTmus.

In conclusion, ERL reduces the potential for inspiratory muscle fatigue in COPD by reducing T0/T0 without affecting FRC and P1.

Pursed-lip breathing (PLB) is a technique used by some patients with chronic obstructive pulmonary disease (COPD) as a means of decreasing dyspnea. PLB provides a variable expiratory resistive load (ERL) imposed by the subject. Whereas ERL with a fixed resistor and PLB are not equivalent in their effects on breathing pattern, they do induce comparable respiratory muscle recruitment responses (29), making it useful to review both techniques together.

The impact of PLB and ERL on the diaphragmatic tension-time index (TTdi) and other parameters in COPD and normal subjects has been studied with conflicting results (6, 11, 15, 21, 22, 29, 30). The TTdi was introduced by Bellemare and Grassino (3) as a means of identifying the fatigue threshold of the dia-

The parameters that comprise TTdi include the mean inspiratory transdiaphragmatic pressure (Pdi) as a fraction of the maximum transdiaphragmatic pressure (Pdimax), as well as the inspiratory time (TI) as a fraction of the total respiratory cycle time (T0) such that TTdi = Pdi/Pdimax × TI/T0, where T0/T0 is the inspiratory muscle duty cycle. The index was found to be related to the diaphragmatic electromyogram (4), which has also been used to identify diaphragmatic fatigue (14). Since its initial description, TTdi has been used to evaluate diaphragmatic function in multiple disease states, including COPD (5, 6).

Measurement of TTdi requires placement of esophageal and gastric balloons, which is moderately invasive, especially for patients who are already dyspneic. A noninvasive tension-time index for all respiratory muscles [TTmus = P0.1/TI × T0.1/T0, where P0.1 is mean pressure developed by the inspiratory muscles, and P1 is the maximal inspiratory pressure at functional residual capacity (FRC) generated at the mouth] has been used in children (11) and adults (25) and recently has been validated in normal and COPD patients (24). According to this method, P1 is estimated from the airway occlusion pressure at 0.1 s (P0.1) as P1 = 5 × P0.1 × TI (11, 24). To make this estimation of P1, the pressure developed by the inspiratory muscles must be assumed to increase linearly during inspiration.

Ramonatxo, et al. (24) found a highly significant correlation between TTmus and TTdi and thus came to the conclusion that the noninvasive tension-time index is a valid means of evaluating potential inspiratory muscle fatigue in patients with COPD. It has been further argued (24) that, because there is a change in the pattern of ventilatory muscle recruitment in COPD from diaphragmatic predominance to rib cage inspiratory muscle predominance (18), and because rib cage muscles can be fatigued independent of diaphragmatic fatigue (10, 35), the noninvasive TTmus rather than TTdi may better reflect inspiratory muscle fatigue in COPD patients. The effect of PLB on TTdi has been described (6), but the effects of either PLB or ERL on TTmus have not been studied. We, therefore, used
TT\textsubscript{mus} to study the effect of ERL on inspiratory muscle performance in COPD patients.

**METHODS**

*Subjects.* Patients with COPD were recruited from our pulmonary clinics in the outpatient department of the Boise Veterans Affairs Medical Center. The diagnosis of COPD was made based on history of smoking, medical history, chest X-ray, physical examination, and chronic airflow obstruction as defined by a forced expiratory volume in 1 s (FEV\textsubscript{1}) $\leq$ 60% of the predicted normal value. Additionally, normal male volunteers with no history of smoking or lung disease took part in the investigation. After the study protocol was explained to all subjects, subjects gave verbal and written consent to participate in the protocol. The study protocol was approved by the Human Subjects Committee of the University of Washington and Research and Development Committee of the Boise Veterans Affairs Medical Center.

*Apparatus for application of ERL.* The apparatus that was used to apply ERL (Fig. 1) consisted of a mouthpiece attached to a T piece with one-way flap valves such that air was inspired through one port and exhaled through the other port. An airflow resistor was placed in-line at the expiratory limb of the T piece, and both the inspiratory and expiratory limbs of the T piece were attached to a pneumotachometer. The pressure-flow characteristics of the airflow resistor are displayed in Fig. 2. The partial pressure of end-tidal carbon dioxide (PET\textsubscript{CO\textsubscript{2}}) was measured near the pneumotachometer with an infrared Datex CO\textsubscript{2} analyzer (standard equipment on the MedGraphics critical care management module). All measurements were taken with and without the expiratory flow resistor in place. The order of testing with or without the resistor was alternated from subject to subject, and the subjects were not aware of what measurements were being taken until after the testing procedure.

*Instrumentation and measurements.* Spirometry was performed according to established guidelines of the American Thoracic Society (1) using a SensorMedics 2200 spirometer (SensorMedics, Yorba Linda, CA). This included measurements of FEV\textsubscript{1} and forced vital capacity (FVC). During each session, a minimum of two forced flow-volume loops of reproducible quality was obtained. If the FEV\textsubscript{1} and FVC values

![Fig. 1. Experimental apparatus used to apply expiratory resistive loading. See METHODS for complete description. Pneumotach, pneumotachometer.](image-url)
were not within 5% or 0.100 liter of one another, one additional measurement was taken. The flow-volume loop with the best FEV₁ and FVC was used.

FRC with and without ERL was measured by nitrogen washout in all normal volunteers with the SensorMedics 2200 spirometer. To measure the FRC with ERL, the airflow resistor was placed on the expiratory port of the SensorMedics 2200 spirometer while we waited for the subject to reach a steady-state FRC and throughout the nitrogen washout period. In six of the normal subjects and in all COPD patients, a Gould 2800 body plethysmograph (SensorMedics) was used to measure FRC with and without ERL. In this case, the airflow resistor was attached to a one-way valve, which was, in turn, connected to the breathing valve of the body plethysmograph such that the subject could inspire normally through the breathing valve but exhaled through the resistor. The subject was allowed to breathe on this apparatus until steady-state FRC and throughout the nitrogen washout period. RPM was used to characterize each COPD patient.

Subjects. One female and 13 male patients with COPD were recruited for the study and gave informed consent (Table 1). In addition, 10 normal male volunteers were studied. The COPD group differed from the normal subjects in that they were significantly older (age range 56–80 yr old for the COPD group and 21–49 yr old for the normal subjects), had a history of smoking [61 ± 18 (SD) yr], had marked airflow obstruction...
TTmus. The effect of ERL on TTmus in COPD patients is demonstrated in Table 2. Specifically, TTmus decreased by 12% \((P = 0.02)\) with ERL. Whereas most subjects had a drop in TTmus, there was some variability, and some actually had an increase in TTmus with ERL (Fig. 3). Figure 3 also demonstrates the TTmus isopleths of 0.27 and 0.33, which, in validation studies (24), correlate with Bellemare and Grassino’s critical TTdi of 0.12 for COPD patients (5) and 0.15 for normal subjects (3). These critical values represent the fatigue thresholds above which subjects cannot persistently maintain their breathing pattern. Several of the COPD patients were breathing near or above the fatigue threshold at baseline, and in general ERL tended to move these subjects to a more favorable TTmus. The drop in TTmus was the result of a prolongation of T E and a reduction in TI and TT. Otherwise, TI, P0.1, and Pbar I were significantly elevated by ERL (Table 2).

In normal subjects, the mean TTmus similarly decreased by 15% \((P = 0.03)\) with considerable variability among subjects (Fig. 4). None of the normal subjects was close to the fatigue threshold \((TTmus = 0.33)\). Again, T E was significantly prolonged, whereas T I remained unchanged. However, in contrast to the COPD patients, P0.1 and Pbar I were significantly elevated by ERL (Table 2).

The baseline TTmus in normal subjects was 56% less than that in COPD patients \((P < 0.001)\) as a result of a higher Pbar Imax in normal subjects \((P < 0.001)\). The other components that factor into the baseline TTmus (T I, T E, Pbar) were not significantly different between the two groups (Table 2).

Table 2. Ventilatory parameters with and without ERL in COPD and normal subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD Patients ((n = 14))</th>
<th>Normal Subjects ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTmus, s</td>
<td>0.211 ± 0.019$</td>
<td>0.185 ± 0.018*§</td>
</tr>
<tr>
<td>T I, s</td>
<td>1.5 ± 0.1</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>T E, s</td>
<td>2.8 ± 0.2</td>
<td>3.7 ± 0.2*†</td>
</tr>
<tr>
<td>T T, s</td>
<td>4.3 ± 0.3</td>
<td>5.3 ± 0.5*§</td>
</tr>
<tr>
<td>T I/T T</td>
<td>0.35 ± 0.01</td>
<td>0.30 ± 0.01‡</td>
</tr>
<tr>
<td>PPI max, cmH2O</td>
<td>3.7 ± 0.3</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>Pt, cmH2O</td>
<td>26.1 ± 1.6</td>
<td>26.7 ± 1.6</td>
</tr>
<tr>
<td>P/Pbar I max</td>
<td>0.61 ± 0.06§</td>
<td>0.62 ± 0.05§</td>
</tr>
<tr>
<td>RR, cycles/min</td>
<td>15.5 ± 1.0</td>
<td>13.3 ± 1.2†</td>
</tr>
<tr>
<td>VT, liters</td>
<td>0.97 ± 0.06</td>
<td>1.04 ± 0.08*§</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>14.4 ± 0.7§</td>
<td>12.8 ± 0.8†</td>
</tr>
<tr>
<td>Vt/T I, l/s</td>
<td>0.66 ± 0.04§</td>
<td>0.70 ± 0.05</td>
</tr>
<tr>
<td>FRC, liters</td>
<td>6.64 ± 0.37§</td>
<td>6.67 ± 0.38§</td>
</tr>
<tr>
<td>SbHb %</td>
<td>92.1 ± 0.8</td>
<td>92.3 ± 0.8</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>27.5 ± 1.6</td>
<td>27.9 ± 1.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; \(n\), no. of subjects. NERL, no expiratory resistive loading; ERL, expiratory resistive loading; TTmus, noninvasive tension-time index of the inspiratory muscles; T I, inspiratory time; T E, expiratory time; T T, total respiratory cycle time; T I/T T, inspiratory muscle duty cycle; P0.1, inspiratory occlusion pressure at 0.1 s; P bar I max, ratio of Pbar I to Pbar I max; RR, respiratory rate; VT, tidal volume; VE, minute ventilation; Vt/T I, mean average inspiratory flow; SbHb, hemoglobin saturation; PETCO2, partial pressure of end-tidal carbon dioxide. *\(P < 0.05\) for NERL vs. ERL; †\(P < 0.001\) for NERL vs. ERL; §\(P < 0.05\) for COPD vs. normal subjects; \%§\(P < 0.001\) for COPD vs. normal subjects.
The baseline indexes obtained without ERL are similar to those found in the validation studies done in normal subjects and COPD patients (24). Ramonatxo et al. (25) also used the technique to demonstrate the absence of any difference in TTmus with and without ERL in normal subjects exercising at 40% of their maximum O2 consumption. However, this is the first use of this method to ascertain the effect of ERL in COPD patients. These noninvasive measurements are similar to Breslin’s (6) more invasive measurements of TTdi in COPD patients using PLB techniques. However, because the TTmus does not require the placement of esophageal and gastric balloons, it is a technique that may better lend itself to the study of subjects with more severe, acute airflow obstruction.

When comparisons are made between TTmus and TTdi, the issue of whether or not one is better than the other must be raised. In fact, Spahija and Grassino (29) looked at the effect of ERL on the TTdi of normal subjects and found that the TTdi remains unchanged, a result that would appear to be different than our finding of a decline in TTmus in normal subjects. Alternatively, the two indexes may better be thought of as measurements of two different muscle groups. The TTdi is an index of diaphragmatic function, whereas TTmus is a better indicator of the output of all inspiratory muscles. Thus a drop in TTmus without a significant change in TTdi in normal subjects treated with ERL may be an indication of improved efficiency of the rib cage muscles without a concomitant improvement in the diaphragmatic efficiency. Others have shown that rib cage muscles and diaphragm function can be partially uncoupled and have concluded that the two muscle groups can be fatigued independently, depending on inspiratory recruitment patterns (10, 35). Martinez et al. (18) have also shown that the pattern of ventilatory recruitment in COPD is one of rib cage inspiratory muscle rather than diaphragmatic predominance, thus leading some (24) to suggest TTmus rather than TTdi as the better indicator of inspiratory muscle fatigue in COPD patients. TTmus may actually be much closer to the rib cage tension-time index (35) with similar fatigue thresholds (24).

The validity of TTmus as a measure of respiratory muscle function rests, in large part, on the assumption that P0.1 provides an accurate assessment of P1 (11). The calculation of P1 from P0.1 assumes a linear rise in respiratory muscle pressure from initiation to termination of inspiration. This is not always the case, and, at least in anesthetized animals and humans, the slope of the inspiratory pressure curve of the occluded airway is often not linear (28, 33, 34). This is especially true at higher RRs. However, whereas the shape of the occluded airway pressure curve is quite variable from subject to subject, the shape of the waveform within any given human or animal subject is quite repeatable (28, 34). Thus, whereas comparisons of repeated mea-
measurements of $P_{0.1}$, $P_t$, and $TT_{mus}$ for any one individual should be reliable, the use of the absolute values to compare different subjects may be somewhat limited. Alternatively, the validation studies of Ramonatxo and colleagues (24) show a significant correlation between $TT_{mus}$ and $TT_{di}$ and various respiratory pressure measurements in both COPD and normal subjects, suggesting that use of $TT_{mus}$ to compare different groups and individuals is indeed valid. This should allow the use of this noninvasive tension-time index to assess the effect of various disease states and experimental protocols on the respiratory muscles. The fact that $TT_{mus}$ measurements do not require placement of esophageal and gastric balloons makes this technique a much easier tool for assessing subjects who are experiencing acute exacerbation of their respiratory disease and may not tolerate more invasive measurements. As with any other index of respiratory muscle function, it does have its limitations, and the effect on $P_{0.1}$ of various disease states, exercise, medications, ERL, FRC, and other factors must always be considered when evaluating $TT_{mus}$ values (33).

The tension-time indexes have been used in large part as a predictor of endurance and fatigue in individual muscles or groups of muscles, especially the diaphragm (3, 4, 10). Specifically, the higher the index, especially if near the threshold values, the closer the muscle group is to fatigue. However, it may be more useful to look at the individual components of $TT_{mus}$ to better understand the effect of ERL on inspiratory muscle function.

Analysis of these components that comprise the $TT_{mus}$ shows that baseline $TT_{mus}$ for COPD patients is significantly higher than that for normal subjects because of the marked difference in $P_{t_{max}}$. In fact, the differences between baseline $T_t$, $T_T$, and $P_t$ are not statistically significant. Similar findings have been demonstrated when $TT_{mus}$ and $TT_{di}$ in COPD patients have been analyzed (5, 24). When looking at the effect of ERL on the components of $TT_{mus}$, it is easily seen that there is a reduction of $TT_{mus}$ in COPD patients only because $T_e$ and $T_T$ are prolonged, whereas the other components remain unchanged. Breslin (6) found that PLB had a similar effect on $T_T/TT$ without changing $P_{di}$ in those with COPD. In contrast, ERL in normal subjects resulted in not only a prolonged $T_e$ but also an elevation in $P_{0.1}$ and $P_t$. This elevation in $P_{0.1}$ and $P_t$ with ERL has been found by others (13, 25) and significantly minimizes the reduction in $TT_{mus}$ seen with ERL in normal subjects. To our knowledge, this is the first time that this contrast between COPD and normal subjects in their response to ERL has been noted. It provides a potential explanation of why PLB is commonly used by some COPD patients and not by those without any lung disease. It should also be noted that the difference in response to ERL between COPD and normal subjects in this study may in part be due to the significant difference in the ages of the two groups.

$RR$, $V_T$, and $V_e$ are also affected by ERL in COPD patients. The decline in RR and $V_e$ and the larger $V_T$ with ERL and PLB have been described by others (6, 30). Reports of the effect of ERL and PLB on these parameters in normal subjects have been mixed (13, 22, 23, 25, 29). Whereas we found similar trends in RR, $V_T$, and $V_e$, none of the changes with ERL in normal subjects was statistically significant or as dramatic as those seen in COPD patients. Our baseline $V_e$ and $V_T/T$ values were higher than those of others (24), which was probably a result of the dead space in the experimental apparatus.

It has been shown that a drop in RR without the use of PLB or ERL reproduces many of the same effects as PLB and ERL (20, 30). The braking action of the inspiratory muscles during exhalation probably accounts for a significant slowing of the RR (12, 27), but PLB and ERL may provide an alternative means of slowing the RR without placing additional demands on the inspiratory muscles. This would be most important during the respiratory muscle fatigue, which can be seen with high levels of ventilation (2, 7, 17), and in COPD patients, who demonstrate lower $P_{t_{max}}$ and higher $TT_{mus}$ (8). Whereas this study does demonstrate a decrease in RR, $TT_{mus}$, $V_e$, and $T_T/TT$ and can, therefore, demonstrate at least some of the potential advantages of PLB and ERL in COPD patients, it does not address inspiratory muscle function during expiration and probably does not fully explain the subjective decrease in dyspnea and objective improvement in gas exchange seen with PLB and ERL. In fact, the greatest decline in workload on the inspiratory muscles may come not from the decline in $T_T/TT$, RR, and $V_e$ but from their being relieved of their expiratory braking duties. This study also does not address the increased demands placed on the expiratory muscles by ERL. How much ERL is adequate to relieve inspiratory muscle fatigue without inducing expiratory muscle fatigue remains unclear but likely varies dramatically, depending on the subject and breathing conditions.

The determinants of diaphragmatic endurance have been reviewed and include not only the tension-time index but also the work rate and lung volume (9, 16, 32). As discussed above, ERL in COPD patients does indeed decrease the tension-time index and, although not directly measured in our study, may decrease the workload on the inspiratory muscles. The third determinant of inspiratory muscle endurance, namely the volume, was evaluated in our study. FRC did not change with ERL in the COPD patients. This finding was similar to that of Thoman et al. (30), who found no change in FRC with PLB or rate-controlled breathing, but was in contrast to the apparent elevation in FRC with ERL and PLB found by others (15, 23). However, Ingram and Schilder (15) did note that, when those COPD patients who routinely used PLB are compared with those who did not, the PLB group had a much smaller degree of FRC elevation with ERL. Like Ingram and Schilder, we also found significant variability in the FRC response to ERL in COPD patients. Thus different FRC findings may be a result of subject selection. Exactly what accounts for the different FRC
response to ERL remains unclear. It is interesting to note a trend toward worse FEV₁ and/or maximal voluntary ventilation in those who had little to no elevation in FRC in both our study and Ingram and Schiller's study. However, no statistically significant correlation could be found in either of the studies because of the small number of subjects studied. A decrease in end-expiratory alveolar pressure due to the increase in Tₑ would be one potential explanation for a decrease or lack of elevation of FRC with ERL.

As demonstrated by others (15, 25, 29), the mean FRC in the normal subjects did increase significantly. This could contribute to a reduction in the inspiratory muscle endurance (32). In addition, the increase in FRC may in itself decrease the Pₒ₂, thereby decreasing the Pt and TTₘus, which otherwise might have been seen with ERL if the FRC had been unchanged in normal subjects. It should also be noted that Pₘₐₓₐₓ was measured only at FRC without ERL. TTₘus calculated with the Pₘₐₓₐₓ measured at the higher level of FRC would likely be higher, because Pₘₐₓₐₓ tends to decrease with elevated lung volumes. Thus the TTₘus in the normal subjects may not have significantly decreased with ERL if the elevated FRC (and therefore reduced Pₘₐₓₐₓ) had been considered.

ERL and PLB have usually been shown to increase arterial PO₂/SaO₂ (6, 20, 26, 31), whereas their effects on arterial PCO₂, PetCO₂, and CO₂ production have been variable (22, 23, 25, 30). Our study failed to show any significant change in either SaO₂ or PetCO₂ with ERL in COPD patients. One potential explanation for this is the increased workload placed on the expiratory muscles with the fixed expiratory resistor. This may have resulted in a higher CO₂ production and O₂ consumption, which, in turn, could have masked any improvement in gas exchange when only SaO₂ and PetCO₂ were measured. The higher dead space of the experimental apparatus may also have affected the PetCO₂.

In summary, we have demonstrated that ERL results in a decline in the TTₘus of COPD patients by reducing the Tᵣ/Tᵣ. It has no effect on the Pt nor the FRC of these patients. This may, in part, explain the use of PLB by these patients. We have also shown that the noninvasive TTₘus is well tolerated by patients with chronic dyspnea and provides a practical means of studying the tension-time index of these patients at baseline and potentially during acute exacerbation of their chronic disease.

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REFERENCES


